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Neuroprotective effects of ginsenosides

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Review

Abstract. Ginseng, the root of the *Panax* species, is a well-known herbal medicine. Traditionally it has been used in Korea, China and Japan for thousands of years. Nowadays it has become a popular and worldwide known health drug. Current scientific studies demonstrate *in vivo* and *in vitro* its beneficial effects in a wide range of pathological conditions such as cardiovascular disease, cancer, immune deficiency and hepatotoxicity. Ginsenosides or ginseng saponins as the active ingredients have antioxidant, anti-inflammatory, anti-apoptotic and immunostimulant properties, which raised speculations that these compounds could positively affect neurodegenerative disorders and delay neuronal aging. Conclusive clinical data in humans are still missing. However, results from animal studies and neuronal cell culture experiments indicate that ginsenosides can counteract and attenuate factors promoting neuronal death as environmental toxins, excitotoxic action of glutamate and rises in intracellular calcium, excessive release of free radicals and apoptotic events. Thus, neuroprotective actions of ginsenosides could come about as a valuable option to slow down neurodegenerative diseases.

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INTRODUCTION

The concept of neuroprotection

The term neuroprotection refers to measures antagonizing and delaying neuronal loss by slowing or blocking processes, which cause death of nerve cells either prematurely or in old age (Gerlach et al. 2000). Generally it refers to phenomena which are antagonizing oxidative stress in nervous tissue. Oxidative stress is defined as the general principle of an imbalance in between the formation and the detoxification of reactive oxygen species in favor of the former. These reactive oxygen species include hydrogen peroxide and such oxygen derived radicals as the hydroxy radical, the superoxide radical and NO. When not sufficiently scavenged, these small molecules may cause DNA-deletions and mutations, lipid peroxidation causing membrane damage, and alterations in proteins are generated.

Radical detoxification processes either involve enzymatic action of superoxide dismutase, glutathione peroxidase and catalase as well as such water soluble antioxidants as ascorbic acid, GSH and cysteine as well as lipid soluble molecules such as tocopherols, coenzyme Q and carotinoids.

Neuroprotective properties have been attributed to a constantly growing number of compounds as receptor agonists (e.g., dopamine agonists – Radad et al. 2005) or a range of such natural compounds as flavonoids or natural medicines (e.g., ginseng, Liu et al. 2006).

Ginsenosides, the active ingredients of ginseng root

Ginseng refers to the roots of several species in the plant genus *Panax* (C.A. Meyer *Araliaceae*). Among them, Panax ginseng is the most widely used being indigenous to Far East countries (most notably Korea and China). Panax ginseng has a medical history of more than five thousand years. The genus name of Panax ginseng "Panax" was given by the Russian botanist C.A. Meyer, and is derived from the Greek words "pan" meaning all and "axos" meaning cure. The species name "ginseng" comes from the Chinese word "rensheng" which means "human" as ginseng roots resemble the human body (Noverino et al. 2000).

Ginsenosides or ginseng saponins represent the principle active ingredients in ginseng and more than thirty different analogues have been identified (Yun 2001). They consist of a gonane steroid nucleus with 17 carbon atoms arranged in four rings. The characteristic biological responses for each ginsenoside are attributed to the differences in the type, position and number of sugar moieties attached by glycosidic bond at C-3 and C-6 (Fig. 1). Based on their structural differences, they can be classified into three categories: the panaxadiol group (e.g. Rb1, Rb2, Rb3, Rc, Rd,

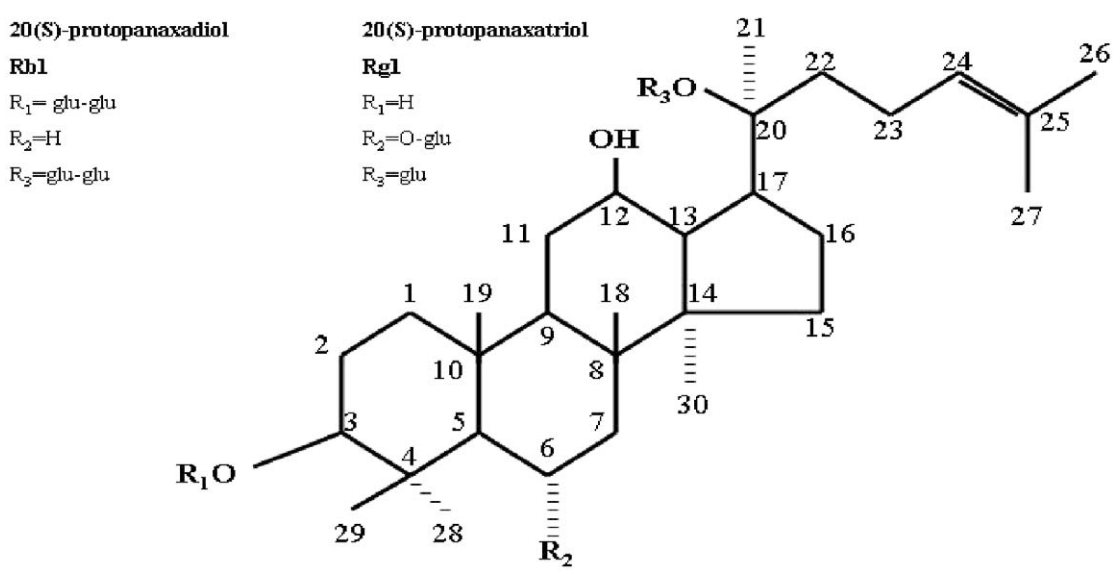

Fig. 1. Chemical structures of both ginsenosides Rb1 and Rg1. Ginsenoside Rb1 is an example for 20(S)-protopanaxadiol type while Rg1 for 20(S)-protopanaxatriol type.

Rg3, Rh2, Rs1), the panaxatriol group (e.g. Re, Rf, Rg1, Rg2, Rh1), and the oleanolic acid group (e.g., Ro) (Wen et al. 1996).

General effects attributed to ginseng

Ginseng products are commonly used as general tonic and adaptogen to help the body to resist the adverse influences of a wide range of physical, chemical and biological factors and to restore homeostasis (Blumenthal 2001). These tonic and adaptogenic effects of ginseng are believed to enhance physical performance including sexual function and general vitality in healthy individuals, to increase the body's ability to fight stress in stressful circumstances and to support resistance to diseases by strengthening normal body function as well as to reduce the detrimental effects of the aging processes (Tyler 1993). Current reviews on pharmacological and biological activities on ginsenosides are recommended for reference (Zhang 2006).

Effects of ginsenosides on cognitive function and decline

The use of herbal medicine, particularly ginseng, for improving cognitive performance has become increasingly popular during recent years and some studies have shown its enhancing effects on learning and memory either in aged and/or brain damaged individuals (Yamaguchi et al. 1996). For example, significant improvement in learning and memory has been observed in aged and brain-damaged rats after local administration of ginseng powder (Kennedy and Scholey 2003). In humans, Terasawa and coauthors (1997) have shown that ginseng or ginseng extract had significant effects on neurological and psychiatric symptoms in aged humans and psychomotor functions in healthy subjects respectively. This positive effect of ginseng on cognition derives from the direct action of ginseng on the hippocampus. Moreover, Shen and Zhang (2003) suggested that the influence of ginsenoside Rg1 on the proliferating ability of neuronal progenitor cells may serve as an important mechanism underlying its nootropic and anti-aging effects particularly on learning and memory. This still appears controversial, as in healthy individuals the regular use of ginseng during long time periods (up to 2 years) did not provide quantifiable beneficial effects on memory performance (Persson et al. 2004).

Ginseng rescues neuronal cells *in vivo*

It has been shown that ginseng and its saponins have a wide range of actions in the central nervous system. These effects include increased neural survival, extension of neurite growth and rescuing of neurons from death due to different insults and deficient supply either *in vivo* or *in vitro*, e.g., in ischemia in gerbils central infusion of ginsenoside Rb1 rescued hippocampal neurons from cellular hypoxia (Lim et al. 1997, Wen et al. 1996).

Ginsenoside effects on pesticides and other environmental toxicants

Due to their presence in the environment and the direct exposure of humans and animals neurotoxic actions for a wide range of pesticides are currently of concern. Though accumulation and long term-low dose toxicity are far from being understood, the action of pesticides as rotenone, polychlorinated biphenyls (PCBs) and fungal toxins can be demonstrated in neuronal cell cultures, where the impact is directed against mitochondrial function or also involves specific receptor action. Interestingly ginsenosides appear to attenuate these effects.

Rotenone as a common household pesticide is a specific and irreversible inhibitor of complex I of the mitochondrial chain (Antkiewicz-Michaluk et al. 2003, Betarbet et al. 2000). Ginsenoside Rg1 showed neuroprotective action, presumably by interacting with glucocorticoid receptors as their receptor antagonists prevented this effect. (Leung et al. 2006). 3-Nitropropionic acid is a compound found in crops contaminated with fungi and causes neurotoxicity both in humans and animals. As the compound induces a selective striatal pathology, it has been widely used as an agent to model Huntington´s disease. Against striatal infusion as well as in striatal neuronal cultures ginseng saponins exerted neuroprotective action, which was found as a reversion of Ca^{2+}-increases and a normalisation of mitochondrial depolarisation (Kim et al. 2006). PCBs as environmental pollutants are highly persistent in nature and some congeners as PCB-52 exert neurotoxic action. Including ginsenosides in the medium reduced lipid peroxidation, apoptotic events and DNA fragmentation caused by this congener (Moon et al. 2006).

Ginsenoside effects in Parkinson's disease models

Agents such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can cause parkinsonian features in man and experimental animals. Prolonged oral administration of ginseng extract G115 significantly prevented neurotoxic effects of MPTP in rodents (Van Kampen et al. 2003). 1-Methyl-4-phenylpyridinium (MPP^+), the active metabolite of MPTP is selectively toxic to dopaminergic neurons in culture. The degenerative changes by MPP^+ as e.g., a loss of dendritic processes is effectively reduced by ginsenoside Rb1 (Radad et al. 2004a).

In order to elucidate the neuroprotective mechanism of ginseng for dopaminergic neurons, several reports demonstrate the inhibitory role of ginseng on MPP^+ uptake in dopaminergic neurons, the suppression of oxidative stress induced by autooxidation of dopamine, the attenuation of MPP^+-induced apoptosis and the potentiation of nerve growth factor action. Ginsenosides inhibited dopamine uptake into rat synaptosomes (Tsang et al. 1985) and consequently ginseng could provide protection against MPP^+ through blockade of its uptake into dopaminergic neurons. Ginsenoside Rg1 may interrupt dopamine-induced elevation of reactive oxygen species or nitric oxide generation in pheochromocytoma cells (Chun et al. 2003).

Glutamate as an excitotoxin may contribute to neuronal death

Excitotoxic events could be important triggers for cell death in the nervous system. Glutamate is a major neurotransmitter in the mammalian nervous system and plays an important role in many physiological functions including brain development and learning (Malenka and Nicoll 1993). On the other hand, glutamate is known to be a potent neurotoxin when present in excess at synapses (Plaitakis and Shashidaran 2000). Glutamate excitotoxicity contributes to neuronal degeneration in acute conditions such as stroke, epilepsy, trauma, hypoxia and hypoglycaemia and chronic neurodegenerative diseases such as PD but also Alzheimer's and Huntington's disease and amyotrophic lateral sclerosis (Lipton and Rosenberg 1994). There is general agreement that glutamate action is Ca^{2+}-dependent and the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors plays a key role in mediating glutamate toxicity (Sattler and Tymiansky 2000). Ca^{2+} loading exceeding the capacity of Ca^{2+} regulating mechanisms could activate several cell death-related genes and pathways (Said et al. 2000). These include calcium-dependent activation of nucleases, lipases, proteases and neuronal nitric oxide synthase, thus increasing oxidative stress (Doble 1999).

Ginsenosides reduce glutamate excitotoxicity *in vitro*

Ginsenosides Rb1 and Rg3 protected cultured rat cortical cells from glutamate-induced neurodegeneration (Kim et al. 1998). In our studies on glutamate excitotoxicity (Radad et al. 2004b), primary dopaminergic neurons from embryonic mouse mesencephala were exposed to a neurotoxic glutamate concentration and protective effects of ginsenosides Rb1 and Rg1 on survival and neuritic growth of the cells were tested. Excessive glutamate promoted the release of lactate dehydrogenase, propidium iodide uptake by the cells and increased the number of nuclei with condensed and fragmented chromatin as apoptotic characteristics. Moreover, glutamate extensively reduced tyrosine hydroxylase immunopositive cells and adversely affected the appearance of their neuronal processes. The toxic effect of glutamate was primarily caused by over-activation of the N-methyl-d-aspartate (NMDA) receptor as treatment of cultured cells with (+)MK 801, a NMDA receptor antagonist, nearly abolished the dopaminergic cell loss and LDH release induced by glutamate. Pre-treating and post-treating with ginsenosides Rb1 and Rg1 to glutamate exposure significantly increased the numbers and lengths of neurites of surviving dopaminergic cells. Thus ginsenosides Rb1 and Rg1 appear to exert partial neurotrophic and neuroprotective functions against glutamate in cell culture (Radad et al. 2004b).

Ginsenosides as neuroprotectants

Reflecting the "*panacea*" status of ginseng a multitude of possible effects may be held responsible for the neuroprotectant effects of ginsenosides. The large variety of ginsenosides, their complex composition, depending on the particular variety of the ginseng plant and the effect of the processing steps to get a final product as white ginseng, red or even black ginseng and not to forget metabolic conversions, make it difficult to focus on a single pharmacological mechanism.

The prominent ginsenosides Rb1 and Rg1 have been most tested, but currently metabolites also gain importance.

Ginsenosides promote cell proliferation and enhance the survival rate of new-born cells. Ginsenosides Rb1 and Rg1 elevated NGF mRNA expression in rat brain (Salim et al. 1997). Ginsenosides have neurotrophic effects, as they reversed the neurotoxic effects of MPP+ through elevation of mRNA expression of NGF (O´Hara et al. 1998). Nonneuronal effects of ginsenosides as stimulating endothelial growth and thus promoting angiogenesis could contribute to neuroregeneration (Huang et al. 2005).

Preserving neuronal function by ginsenosides, as in improvement of learning and memory and counteracting stress and depression, appears to be by modulating neuronal, e.g., hippocampal activity. Neuroprotective effects in ischemia models could reflect energetic sparing by preserving ATP stores. A rise of free radicals due to environmental toxins and mitochondrial dysfunction can be counteracted by different ginsenosides, given their different potencies as antioxidants or free radical scavengers. In vitro the orders of antioxidative ability are Rc > Rb1 and Re > Rd > R1 > Rg1 > Rb3 > Rh1, respectively (Liu et al. 2003).

Aging causes suppression of the antioxidative defense systems and accumulation of lipid peroxidation products. In early senescent mice ginsenoside-Rd attenuates the oxidative damage, which may be related to the intervention of the GSH/GSSG redox status (Yokozawa et al, 2004). Membrane stabilizing effects, such as physicochemical properties adding to cell survival, could be relevant for ginsenoside action. The increment found with ginsenoside Rg1 has been viewed as part of Rg1´s antiaging action (Li and Zhang 1997). Estrogen actions of ginsenosides, so far have not been explicitly correlated to brain and neuronal function, but mainly to anti-tumor action (Chan et al. 2002).

Most effects of ginsenosides are related to their NMDA-receptor actions, counteracting excitotoxicity by glutamate. In particular ginsenoside Rg3 inhibits both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors (Kim et al. 2002, Kim and Rhim 2004) which could be relevant to many neurological disorders particularly brain ischemia, trauma, stroke, and seizures (Choi and Rothman 1990). Inhibition of NMDA and non-NMDA receptors by ginsenosides resulted in a reduction of Ca^{2+} over-influx into neurons and thus protected cells from neurodegenerative processes evoked by Ca^{2+} overload (Liao et al. 2002).

Counteracting neuroinflammatory processes could well be another potential for specific ginsenosides.

Anti-inflammatory activity of ginsenoside Rb1, and its metabolite compound K, produced by intestinal bacteria, on lipopolysaccharide (LPS)-stimulated murine macrophages, were studied. Compound K potently inhibited the production of NO and prostaglandin E2, reduced the expression levels of the inducible NO synthase (iNOS) and COX-2 proteins, and prevented the activation of NF-kB (Park et al. 2005).

Antitapoptotic effects have been tested for ginsenosides. Ginseng attenuated MPP^+-induced apoptosis as it decreased the intensity of MPP^+-induced DNA laddering in PC12 cells and ginsenoside Rg1 had a protective effect against MPTP-induced apoptosis in the mouse substantia nigra. This anti-apoptotic effect of ginseng may be attributed to enhanced expression of Bcl-2 and Bcl-xl, reduced expression of bax and nitric oxide synthase, and inhibited activation of caspase-3 (Chen et al. 2002, Kim et al. 2003).

CONCLUSIONS

Recent experimental evidence provides detailed indications of neuroprotective properties of ginsenosides in cell culture systems and animal studies. Considering the large number of structural analogues of ginsenosides, controversial effects and complex additive interactions have and had to be expected. The approach to use of ginsenosides to affect ongoing chronic processes in neurodegenerative and aging diseases as PD, Alzheimer disease and neuronal degeneration due to ischemic and neuroinflammatory events, is tempting, based on experimental data. A long medical history of these compounds and the relative lack of side effects make them additionally attractive. Yet, though such aspects maybe stimulating, it is clearly a long way from in vitro data to a proven neuroprotective potential in human disease. It will require validated data from the clinic and here particularly imaging techniques and long term follow-up, as to actually prove whether the postulated neuroprotective action of ginseng and/or its saponins have this desired effect in neurodegenerative disorders.

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